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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,923	12/21/2001	Brian Gaither Bates	AM100369	9899

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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,923	BATES ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,13-19 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,13-19 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-17-04 has been entered.

2. The amendment filed 9-17-04 has been entered into the record and has been fully considered.

3. Claims 1, 5, 13-19 and 36 are pending.

4. The declaration under 37 CFR 1.132 by Kamalakar Gulukota has been entered into the record and has been fully considered. The declaration is sufficient to overcome the rejection of claims 1-11, 14-19 and 36 based upon Wong et al., US Patent Application Publication US 2002/0142952, filed 3-29-01 and published 10-3-02, as the invention is not "by another".

5. The Examiner notes that the Takahashi, Walker and Tatarczynska references were not received in Applicant's communication of 5-6-04 or properly made of record. Thus, the references and arguments thereto have not been considered further. Copies of the Romano 1996, Romano 2001, Spooren, and Bordi references were received and have been fully considered.

6. The evidence of ATCC deposit under the Budapest treaty of cDNA clone Y1176 as deposit designation PTA-2775 is acknowledged. Applicant's referral to such deposit

on Dec. 12, 200 is noted in the specification at p. 11.

7. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

8. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

Election/Restriction

9. Applicant's election of Group I, claims 1-19 and 36 in the Paper of 11-13-03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

10. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1, 5, 13-19 and 36 of this application. In particular, the priority application is not sufficient as utility is not established and hence the requirements of 35 USC 112 are not fairly met, see utility rejection as noted below. The Examiner further notes Applicants traversal of the utility rejection relies in part upon the disclosure of dimmer formation between mGluR5 and mGluR5M as disclosed at p. 71 of the specification. However, it is noted for the record that dimmer formation is not apparent within Applicant's priority document. Accordingly, should

utility hinge upon such disclosure, priority cannot be granted until the filing date of 12-21-01. Therefore the effective filing date awarded instant claims is the filing date of instant application 12-21-01.**Claim Rejections - 35 USC § 101**

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

12. Claims 1, 5, 13-19 and 36 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

The specification discloses at pp. 1-5, that the invention is related to nucleic acids and peptides referred to as metabotropic glutamate receptor subtype modulatory proteins (also referred to herein as the mGluR5M proteins or the mGluR5M family. The peptides are noted to be related by homology to mGluR5 receptor proteins, particularly in N- and C-terminal regions, hence the name. In addition, the molecules, mimics and/or modulators are noted to be useful in regulating a variety of cellular processes. For example the specification notes uses related to screening assays, detection assays, chromosomal mapping, tissue typing, prevention, forensics, diagnostics, prognostics, monitoring in clinical trials, prophylaxis, therapeutics and pharmacogenomics, see in particular pp. 50-65. In particular, pp. 10 of the specification notes that, "a "mGluR5M activity", "biological activity of mGluR5M" or "functional activity of mGluR5M" includes modulation (e.g., enhancement or inhibition) of glutamate receptor functions and/or activities, in particular, metabotropic glutamate receptor functions and/or activities (e.g.,

mGluR5 functions and/or activities)... In a preferred embodiment, a mGluR5M activity is at least one of the following activities: (1) modulation of G protein linked second messenger signaling pathways (e.g., modulation of diacylglycerol and/or inisitol triphosphate-mediated signaling pathways), for example, signaling pathways involved in neuronal cell signalling and nervous system function; (2) modulation of glutamatergic transmission; (3) modulation of neuronal excitability; (4) regulation of synaptic transmission; (5) modulation of neurotransmitter release (e.g., glutamate release); (6) regulation of voltage-dependent and/or voltage-independent and/or ligand-gated ion channels (e.g. , K+ channels or Ca2+ channels); (7) regulation of neuronal development (e.g., regulation of neuronal differentiation, migration and/or survival in the developing brain); (8) modulatoin of nervous system function; and (9) modulation of neurodegenerative processes (e.g., acute or chronic neurodegenerative processes). In yet another embodiment, a mG1uR5M activity is "modulation of mGluR5 dimerization (e.g., mG1uR5a and/or mGluR5b dimerization) and/or dimerization of other mGluR family members (e.g., mGluR1 dimerization)." In addition, the functions noted are said to be useful for example in, "treating, for example, neurodegenerative disorders and/or diseases (e.g., motor neuron disease (MND), amyotrophic lateral sclerosis (ALS), Huntington's chorea, Parkinson's disease and Alzheimer's disease), stoke, the brain damage occurring acutely after status epilepticus, cerebral ischemia or tratumatic brain injury and/or movement disorders. "

Yet the specification provides no specific and detailed information as to the noted laundry list of possible activities, functions and uses for the specific mGluR5M identified

molecules of SEQ ID NO's:1-3. The specification fails to exemplify any specific and substantial use of the claimed nucleic acids and/or protein encoded thereby. In particular, the significance of the molecule, its functions, effects and substantial utility are lacking. While the specification contemplates the various reagents as useful in the noted molecular techniques of experimentation, such utilities are not specific or substantial because the uses merely rely on the inherent properties of any nucleic acid to hybridize (bind) and/or encode and any peptide to bind and/or stimulate an immune response. The uses stem from the broad generic class of properties applicable to any nucleic acid or peptide molecule. Thus, the disclosed nucleic acids and peptides merely constitute research reagents for further experimentation to discover their "real-world" use. The contemplated uses also do not constitute well-established utilities because their functional significance has yet to be established. The peptides are merely disclosed as being related to glutamate receptor proteins and neuronal cell function and/or cell signaling in general. Yet there is no known sequence structure or function disclosed or recognized as being related to any of a multitude of neurological or neuron associated functions. In addition, the specification does not teach any conserved nucleic or amino acid positions critical to a particular neuron activity, function or phenotype. The biological significance remains to be established such that the artisan can use the peptides and/or nucleic acids to provide public benefit. No "real world" utility is disclosed.

As recognized by Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, the skilled artisan is well aware that there is an unpredictable nature in the ability of

encoding nucleic acids to predict structural and functional activities for any particular protein or protein family, and that even when highly homologous and conserved residues are known only experimental research can confirm the artisan's best guess, see in particular Skolnick, abstract and Box 2. Moreover, Schoepp et al., notes different function even amongst metabotropic glutamate receptors in relation to brain function and pathology, see in particular TIPS, 14(1):13-20, Jan. 1993. Thus, the assignment of instant SEQ ID NO's: 1-3 as mGluR5M molecules and the brief mention of its' relationship to glutamate receptors in general, fails to define a specific or substantial asserted utility or well-established utility for the claimed sequences.

Applicants traverse in the response of 5-6-04. In particular, Applicants note the teachings of Exhibits A-D; Romano et al., 1996 and 2001, Spooren and Bordi. Applicants note the similarity of their mGluR5M isolated sequence to that of mGluR5, tissue expression as in Example 1 and property of dimerization as at Table 1, p. 71. Applicants further note assays to identify molecules that modulate dimerization of mGluR5 and mGluR5M and that this utility is specific. Applicants note that the binding domain is within the N-terminus, that homodimers are functionally relevant and therapeutically important as in Walker, Tatarczynska and Spooren. Thus Applicants assert utility is substantial and credible for identifying compounds which modulate dimmer activity.

Applicant's arguments submitted 5-6-04 have been fully considered but are not persuasive. The Examiner notes that the Takahashi, Walker and Tatarczynska references were not received in Applicant's communication of 5-6-04 or properly made

of record. Thus, the references and arguments thereto have not been considered further. Copies of the Romano 1996, Romano 2001, Spooren, and Bordi references have been received and have been fully considered. Assays to identify molecules that modulate the noted dimerization are not viewed as providing a specific and substantial asserted utility or well established utility for the claimed invention. In particular, the utility is dependent upon experimental research testing for which no predictable outcome is provided. Specifically, neither the specification nor art teach the significance of mGluR5:mGluR5M dimerization or the significance of any molecule capable of modulating such interaction. As no basis for screening or outcome is provided, utility is not established. As previously noted mGluR5 is hypothesized to play a role in any number of neuronal and non-neuronal signaling events. Yet neither the art nor the specification teach a particular role for the claimed sequences in modulating such activities either in a positive or a negative fashion. For example, Spooren notes a number of mGluR5 antagonists for which different activities are noted, see in particular p. 336. Yet the specification and art fail to evidence any role for instant sequences in modulating particular function. While the references note dimerization events, the significance of the dimmers is not established nor any effect of modulating them. Hence relevance, significance and utility cannot be established.

Applicants argue in the response of 9-17-04 as substantially of record.

Applicant's arguments in the response of 9-17-04 have been fully considered but are not persuasive. In particular, Applicants present arguments with Exhibits A-P detailing evidence with respect to Group I glutamate receptors mGluR5 and mGluR1.

The Examiner acknowledges receipt of the noted references. In particular, evidence is noted with respect to glutamate receptor homodimer formation, known agonists and antagonists of the receptors and noted functions of the receptors within in vitro and within in vivo model systems. Such evidence is specific to either mGluR5 or mGluR1 of the prior art, but not for instantly claimed mGluR5M of SEQ ID NO:2.

While the specification does evidence that mGluR5 binds mGluR5M as disclosed at p. 71 of the specification, neither the art of record, exhibits nor specification detail any effect of mGluR5M on dimer formation or effect on mGluR5 receptor activity and/or function either in vitro or in vivo. Similarly, neither the art of record, exhibits nor specification detail any effect on binding of any natural ligand, agonist or antagonist to either mGlur5M of SEQ ID NO:2, in homodimer formation with itself (mGluR5M:mGluR5M) or heterodimer formation with mGluR5 (mGluR5M:mGluR5). Specific function of mGluR5M itself is not disclosed or established. Accordingly, neither specific and substantial asserted utility nor well established utility, nor any functional significance is evidenced or established such that any contemplated screening assay would be reasonably assured or expected to provide for any predictable and/or useful outcome, particularly with respect to providing compounds of predictable use, outcome and/or function.

The mere ability to perform screening assays with any identified compound is not sufficient to provide utility for an invention for which no basis of predictable outcome is provided. Here the assays are merely a means for discovering the peptides functional significance either alone or in combination with mGluR5 via any conceivable means of

experimental manipulation i.e., contemplated as screening. What is missing here is the basis for a specific manipulation of reagents such that the artisan would be reasonably assured the arrival of a population of screened compounds for which the artisan could have a reasonable expectation of specific and substantial function, effect, or significance for suitable use. Yet here none is provided because any effect of mGluR5M on mGluR5 activity is presumption and/or speculation.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 5, 13-19 and 36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

15. Claims 17-19 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors

relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Claims 17-19 and 36 recite a "host cell" generically. Instant specification describes transgenic cells and transgenic organisms as well as contemplates such in gene therapy applications. The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

While the specification is enabling for contact with isolated cells, and the transformation or transfection of isolated cells to express the mGluR5M protein via nucleic acid and vector delivery, the specification fails to teach suitable administration such that any suitably transgenic, transformed or gene vector therapy administered organism may be suitably screened. What is lacking is a description of the proper construct and transformation or transfection procedures as well as mechanisms for assessing mGluR5M activity in vivo, including in humans and in transgenic humans as encompassed by the claims. Those skilled in the art recognize that such technology is currently beyond scope. In particular, Marshall "Gene Therapy's Growing Pains". Science, Vol. 269 (1995), pp. 1050-1055, Orkin et al. "Report and recommendations of the panel to assess the NIH investment in research on gene therapy". (1995). pp. 1-25, and Verma, I. M., et al. "Gene therapy-promises, problems, and prospects". Nature, Vol.

389 (September 1997), pp. 239-242, each denote significant troubles associated with transgenic and in vivo gene therapy approaches to the assessment of in vivo methods and treatments.

The specification fails to provide any exemplary evidence for conducting such screening approaches in vivo, using either transgenic or gene therapy treated cells within an organism. Since the scope of "host cell" is deemed to be so inclusive of transgenic organisms, including human as provided by direct guidance within the specification, the scope of enablement provided by the specification is not commensurate in scope with the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation. Amendment to "isolated" cells is recommended.

Status of Claims

16. No claims are allowed.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should

applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

SHARON L. TURNER, PH.D.
PATENT EXAMINER

Sharon L. Turner, Ph.D.
December 29, 2004